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HyperCVAD for VAD-Resistant Multiple Myeloma

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More effective and safer regimens are needed for patients who have advanced multiple myeloma resistant to or relapsing despite prior treatment with alkylating agents and VAD. We treated 58 such patients using the combination of twice daily cyclophosphamide (total dose 1.8 g/m^2) and VAD (hyperCVAD). Treatment was given to outpatients followed by G-CSF at 5 μg/kg/d until granulocyte recovery. Twenty-three patients responded (40%), with a median duration of granulocyte depression to less than 500/μl of 4 days and a mortality rate of 2%. The median survival time for all patients was 15 months, and the median remission time of responding patients was 8 months. Patients who had low LDH, low B_2M, or primary resistant disease lived significantly longer than patients without these features. The combination of fractionated cyclophosphamide and VAD provided an effective and safe rescue treatment for many patients who had advanced myeloma resistant to standard therapies. © 1996 Wiley-Liss, Inc.

Key words: chemotherapy for myeloma, resistant multiple myeloma, VAD

INTRODUCTION

Few effective treatments are available for patients who have advanced multiple myeloma that is resistant to both alkylating agents and vincristine-doxorubicin-dexamethasone (VAD). Myeloablative therapy for myeloma has been associated with significant morbidity and limited sustained effect against late-phase disease [1,2]. Several useful regimens of high-dose alkylating agents have been associated with significant toxic effects and therefore have been restricted to younger patients in good medical condition [3–5].

In an effort to develop an effective but less toxic therapy for patients with VAD-resistant disease, we studied a combination of high-dose fractionated cyclophosphamide with vincristine, doxorubicin and dexamethasone (hyperCVAD). Fifty-eight consecutive patients who had advanced and resistant myeloma and who had not received a prior intensive alkylating agent program were treated on an outpatient basis. This regimen was given regardless of age, performance status or organ dysfunction, with daily granulocyte colony-stimulating factor (G-CSF) and prophylactic antibiotics during the neutropenic period. The goal was to achieve an acceptable frequency of response with few complications.

MATERIALS AND METHODS

Clinical Features

Fifty-eight consecutive patients who had multiple myeloma resistant to both standard melphalan-prednisone and VAD chemotherapy were treated. There were no exclusions because of age, performance status, or the presence of other medical disorders. The median age was 58 and 14 patients were older than 65. The myeloma protein type was IgG in 47% of patients, IgA in 34%, and only light chains in 19%. Poor risk factors, such as a high serum level of lactate dehydrogenase (LDH >300 U/l, normal <225 U/l) or beta$_2$microglobulin (B_2M > 4.0 mg/l), were present in 52% of patients (Table I).

In 25 patients, the disease was relapsing after a previous remission despite continued chemotherapy with VAD (resistant relapse) (Table I); hyperCVAD was third-line or more therapy for all patients. Primary resistant disease that had not responded to any prior therapy, including

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TABLE I. Patient Characteristics

	HyperCVAD (1993–1994)	Cyclophosphamide-etoposide (1990–1993)
No. patients	58	72
Median age (range)	58 (40–76)	56 (39–71)
Male (%)	59	58
Laboratory studies (%)		
Hemoglobin <8.5 g/dl	26	24
Creatinine >2.0 mg/dl	12	14
Calcium >11.5 mg/dl	15	20
B_2microglobulin >4.0 mg/l	43	55
LDH >300 U/l	22	22
Disease status (%)		
Primary resistance	57	74
Resistant relapse	43	26

VAD or intermittent high-dose dexamethasone, affected 33 patients. HyperCVAD was second-line therapy for 15 patients and third-line or more therapy for 18 patients. Primary resistance included 3 patients with tumor growth of at least 25%, 11 patients with stable disease as defined by less than 25% tumor reduction, and 19 patients with a prior tumor reduction of 26–70% that was insufficient to consider responsive. The median interval from initial chemotherapy was 9 months for all patients who had primary resistant disease (range 3–42 months) and 30 months for those who had relapsing myeloma (range 9–231 months).

Treatment

A central venous catheter was inserted through an antecubital vein by the outpatient nursing service. Treatment consisted of cyclophosphamide (300 mg/m^2/i.v.) over 3 hr every 12 hr for 6 doses on days 1 through 3 (total dose = 1,800 mg/m^2) with oral fluids of at least 2.0 l/day; mesna was given simultaneously by continuous infusion at a dose of 600 mg/m^2/day for 3 days. Twelve hours after the completion of cyclophosphamide, vincristine (2.0 mg) and doxorubicin (50 mg/m^2) were given by continuous infusion over 48 hr; on day 11, vincristine (2.0 mg) was given by rapid i.v. injection. Dexamethasone (20 mg/m^2 p.o.) was administered in a single morning dose for 5 days beginning on day 1 and for 4 days beginning on day 11. G-CSF was started on day 6 at a dose of 5 ug/kg/day sc and repeated daily until the patient's granulocyte level exceeded 2,000/μl for 2 consecutive days. Between days 8 and 18, all patients received ciprofloxacin (500 mg p.o. twice daily), fluconazole (100 mg p.o. daily), and acyclovir (200 mg p.o. three times daily). Patients with fever (>38.3°C) or any sign of serious infection were hospitalized and were administered broad-spectrum i.v. antibiotics. Patients received a second course of hyperCVAD provided there had been a 50% reduction of myeloma protein. Responding patients were maintained on oral cyclophosphamide (125 mg/m^2 every 12 hr) and dexamethasone (20 mg/m^2 each morning) for 5 days every 5 weeks. Eight patients received subsequent myeloablative treatment with autologous blood stem cell transplantation either for persistent resistant disease (seven patients) or to consolidate remission (one patient) [6].

Response and Survival

Response was defined as a 75% or greater reduction of serum myeloma protein production, a 95% or greater reduction of Bence Jones proteinuria and decrease of bone marrow plasmacytosis to less than 5% for at least 2 months [7]. The life table method was used to calculate survival from the onset of therapy, and to assess remission time from the onset of remission to the earliest sign of relapse. Chi-square tests were used to compare response rates and Wilcoxon tests to compare remission and survival data.

RESULTS

Response

Twenty-three of the 58 patients responded to treatment (40%, 95% confidence interval 27–53%), including one patient for whom immunofixation studies showed disappearance of serum myeloma protein. The median tumor halving time for responders was 0.6 month (range = 0.2–2.0 months), and a remission was recognized in all but 3 patients within 2 months. In all responding patients, soft tissue masses disappeared, hypercalcemia reversed, and anemia improved.

Toxicity

HyperCVAD was well tolerated and only one patient died of a treatment-related complication (2%) (Table II). Granulocytes fell to less than 500/μl in all patients and then recovered to this level after a median of 4 days (range 1–15 days), and on a median day 15 after the start of treatment (range 12–22 days). Platelet levels fell to less than 20,000/μl in 35% of patients, with recovery to 50,000/μl after a median of 5 days.

TABLE II. Outcome and Complications Following Chemotherapy

	HyperCVAD	Cyclophosphamide-etoposide	*P*
Disease Outcome			
Response rate (%)	40	35	n.s.*
Median remission (months)	8	10	n.s.
Median survival (months)	15	11	n.s.
Major toxicities			
Early death (%)	2	6	n.s.
Hospitalization (%)	34	93	<.01
Median days granulocytes <500/μl	5	9	<.01

*n.s., not significant.

Thirty-four percent of patients required hospitalization for a median of 7 days for treatment of documented or presumed infection (17 patients), hyponatremia (two patients), or severe ileus (one patient). Among the 17 patients admitted with fever, 13 had no apparent cause and four had pneumonia; a pathogenic organism was cultured from blood or sputum in two patients (*Escherichia coli, S. aureus*). All but one responded to intravenous broad-spectrum antibiotics concurrent with granulocyte recovery. Alopecia occurred in 83% of patients and 22% developed symptoms of mild neuropathy attributed to vincristine. Mild mucositis developed in five patients and no side effects were attributed to G-CSF. With a previous cyclophosphamide-etoposide combination given to a similar cohort of patients, the treatment-related mortality rate was 6%, granulocyte levels fell below 500/μl for a median of 9 days, and hospitalization was required for 93% of patients (Table II) [5].

Survival and Prognostic Factors

The median survival was 15 months for all patients, 10 months for those with resistant relapse, and projected at 22 months for patients with primary resistance. After major prognostic factors were found to be similar for the 58 patients who received hyperCVAD and the 72 comparable patients treated previously with cyclophosphamide-etoposide (Tables I, II), both groups were combined for further analysis of these factors.

Twenty-two percent of the 130 patients showed a high serum LDH level (>300 U/l) with normal liver function and no other clinical explanation for the elevation than myeloma. This feature was associated with resistance to treatment and very short survival (Table III, Fig. 1). There were no significant differences in survival for patients with high or low LDH who received hyperCVAD or cyclophosphamide-etoposide.

Among 101 patients with lower LDH levels (<300 U/l), no features were associated with resistance to treatment. However, an elevated B_2M (>4.0 mg/l) was associated with significantly shorter remission and survival times (Table III, Fig. 2); there were no significant differences in survival for patients with high or normal B_2M who received hyperCVAD or cyclophosphamide-etoposide. Among 53 patients with both low LDH and B_2M, resistant relapse was associated with significantly shorter remission and survival times (Table III, Fig. 3).

DISCUSSION

This paper describes an effective regimen of acceptable toxicity for patients who have VAD-resistant multiple myeloma. The program was designed for outpatients and G-CSF was preferred to GM-CSF to reduce the duration of granulocytopenia with a cytokine that has been associated with fewer side effects [8]. Cyclophosphamide was given twice daily because this schedule appeared to increase the response rate for acute lymphocytic leukemia and Burkitt's lymphoma, possibly because of a greater effect of fractionated treatment against dividing cells [9,10]. Cyclophosphamide given daily for 4 days also appeared superior to a single injection for multiple myeloma [11,12]. Our program of twice-daily cyclophosphamide with VAD induced responses in 40% of patients who had multiple myeloma that was resistant to prior therapies that usually included VAD, a frequency similar to that induced by high-dose cyclophosphamide-etoposide [5]. These treatments were dissimilar and were given to consecutive patients during different time periods. While the results were similar, any meaningful comparison of the 2 treatments is not justified and would require a concurrent, controlled trial. Yet, the consistent results were supported by the cross-resistance observed in eight of nine patients with resistant disease excluded from the study who were treated sequentially with cyclophosphamide-etoposide and then hyperCVAD. The activity of hyperCVAD against disease resistant to VAD suggests that high-dose fractionated cyclophosphamide accounts for most of the antitumor effect and justifies current trials of higher doses of fractionated cyclophosphamide alone.

Despite the inclusion of more older patients, the hyperCVAD regimen was reasonably well tolerated; only one patient died as a result of treatment, and hospitalization for complications was required less than one-half as frequently as after cyclophosphamide-etoposide. The re-

TABLE III. Major Prognostic Factors Affecting Outcome

	No.	Response (%)	P	Remission (median months)	P	Survival (median months)	P
All patients	130	36		9		12	
LDH (U/l)							
<300	101	43	<.01	10	<.01	18	<.01
>300	29	14		3		5	
LDH <300 U/l							
B_2M (mg/l)							
<4.0	53	45	n.s.*	29	<.01	25	<.01
>4.0	48	40		7		11	
LDH <300 U/l + B_2M <4.0 mg/l							
Primary resistant	33	46	n.s.	36	<.01	42	<.01
Resistant relapse	20	45		6		14	

*n.s., not significant.

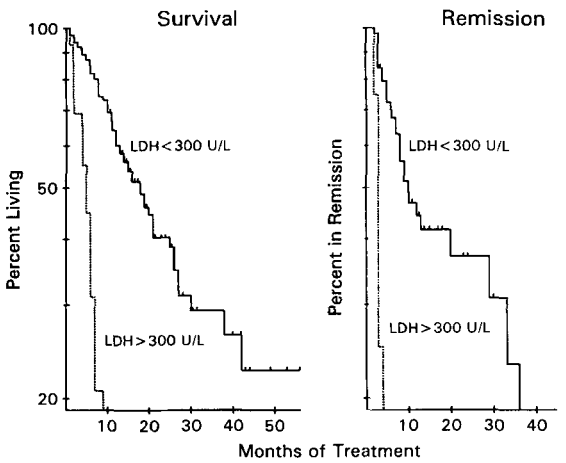

Fig. 1. Survival and remission times for 130 patients according to LDH level. The median survival was 5 months with LDH >300 U/l and 18 months with LDH <300 U/l.

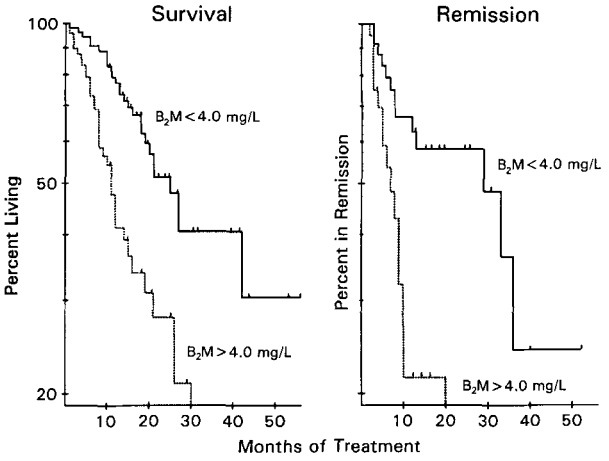

Fig. 2. Survival and remission times for 101 patients with LDH <300 U/l according to B_2M level. The median survival was 11 months with B_2M >4.0 mg/l and 25 months with B_2M <4.0 mg/l.

duced toxicity was attributed mainly to the shorter duration of severe granulocytopenia and the less frequent thrombocytopenia, so that most patients were treated as outpatients. Possible benefits from the substitution of G-CSF for GM-CSF and the administration of prophylactic antibiotics were not clear.

To identify patients who were more likely to have a favorable outcome, we examined the prognostic factors of 130 consecutive and comparable patients who had myeloma resistant to VAD and who received either hyper-CVAD or cyclophosphamide-etoposide. Patients who had a high LDH level rarely benefitted from therapy or qualified for myeloablative treatment, consistent with the inherent resistance to treatment and poor prognosis associated with this disease feature [13]. Alternative investigative therapies are preferable for such patients. Although myeloma in resistant relapse responded frequently, remission and survival times were much shorter than those for comparable patients who had primary resistant disease. Intensive therapy for relapsing disease should be offered to selected patients after careful review of the potential risks and limited benefit for most patients. The short remission after treatment for resistant relapse was similar to that observed after myeloablative therapy [2]. One explanation for the initial sensitivity but early recurrence of disease in resistant relapse could be the evolution with time of more resistant and proliferative subclones [14]. Relapsing myeloma has a higher growth fraction and more colony-forming cells on in vitro culture studies [15,16], features that could account for the short remission and rapid tumor regrowth of relapsing disease despite the more intensive therapy.

Many patients who had primary resistant disease responded to hyperCVAD with a long remission time, but no further prolongation of survival resulted after additional

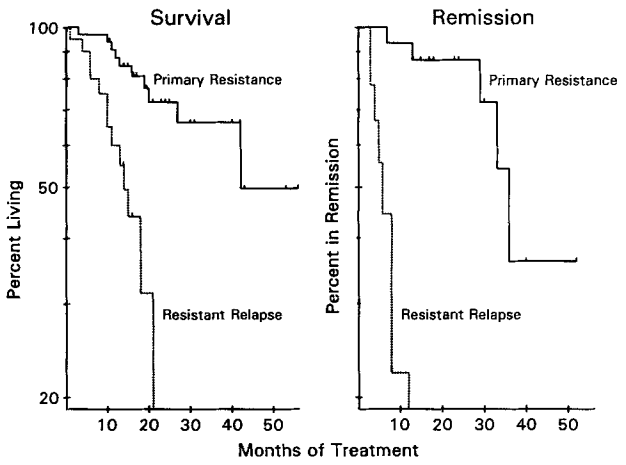

Fig. 3. Survival and remission times for 53 patients with both LDH <300 U/l and B_2M <4.0 mg/l according to disease status.

myeloablative consolidation therapy [2]. Should the disease remain resistant to hyperCVAD or a similar treatment, myeloablative therapy has often been effective in reducing the myeloma, confirming the ease by which apparent tumor resistance can be overcome by progressively higher doses of alkylating agents [3,17]. Thus, hyperCVAD provides an effective treatment of acceptable toxicity that should be considered for all patients with primary resistant myeloma regardless of age or performance. This treatment also constitutes a useful priming therapy for blood stem cell harvest in support of myeloablative treatment when that procedure is indicated [17].

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